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BAY 63–2521, an oral soluble guanylate cyclase stimulator, has a favourable safety profile, improves cardiopulmonary haemodynamics and has therapeutic potential in pulmonary hypertension

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Background

BAY 63–2521 is an oral soluble guanylate cyclase (sGC) stimulator that acts independently of nitric oxide (NO). It targets the reduced form of sGC, and enhances the sensitivity of the enzyme to low levels of bioavailable NO. Phase I clinical trial results suggest that BAY 63–2521 has a favourable safety profile in healthy volunteers. This proof-of-concept study evaluated BAY 63–2521 in patients with moderate-to-severe pulmonary hypertension (pulmonary vascular resistance [PVR] > 300 dyn·s·cm^{-5}).

Materials and methods

This two-part non-randomized, non-blinded, single-site study assessed safety, tolerability, cardiopulmonary haemodynamics, gas exchange and ventilation-perfusion mismatch (VQM). Tolerability of 2.5 mg and 5 mg total doses of BAY 63–2521 was evaluated in 2 × 2 patients given hourly incremental doses (0.5 + 1 + 1 mg = 2.5 mg; 1 + 2 + 2 mg = 5 mg). Further evaluation of 1 mg and 2.5 mg doses was performed in 15 patients and included Swan-Ganz haemodynamics, multiple inert gas elimination technique (MIGET) and blood gas analysis. Results were compared with peak intervention values for inhaled NO (iNO) (8–20 ppm) and one-time post-NO-intervention baseline values. Adverse events (AEs), vital signs, electrocardiograms (ECGs) and laboratory values were monitored.

Results

Baseline measurements in the 2.5 mg group were 42.1 ± 11.3 mmHg mean pulmonary arterial pressure (mPAP), 566 ± 209 dyn·s·cm^{-5} PVR, 133 ± 20 mmHg systolic blood pressure (SBP), and 2.74 ± 0.82 L/min/m^2 cardiac index. BAY 63–2521 was well tolerated up to 2.5 mg, while 5.0 mg caused asymptomatic hypotension in one patient. Six mild AEs (three of which were attributed to BAY 63–2521) occurred in 4 of 19 patients, all resolving by study completion. No serious AEs occurred. BAY 63–2521 had no clinically relevant effects on vital signs, ECGs or laboratory values. No major changes were noted in blood gases or VQM. BAY 63–2521 dose-dependently (1

Table 1: Haemodynamic effects of BAY 63–2521, 2.5 mg

	SBP (mmHg)	SVR (dyn·s·cm^{-5})	mPAP (mmHg)	PVR (dyn·s·cm^{-5})	Cardiac index (L/min/m^2)
vs baseline	-28.6***	-545.9***	-5.1**	-168.1*	0.95***
Vs iNO	-25.7***	-541.5***	-3.1	-132.9*	0.89***

*P < 0.05; **P < 0.005; ***P < 0.0001

mg and 2.5 mg, P < 0.0001 each) reduced mPAP, PVR, SBP, systemic vascular resistance (SVR), and increased the cardiac index (Table 1), while maintaining mean SBP above 110 mmHg. These effects were significantly greater than those of iNO for SBP, SVR, PVR and cardiac index, and approached significance for mPAP. Effects correlated closely with plasma concentrations.

Conclusion

BAY 63–2521 has a favourable safety profile and does not alter gas exchange or VQM at single doses up to 2.5 mg in patients with moderate-to-severe pulmonary hypertension. This agent improved all main haemodynamic parameters in a dose-dependent manner and to a greater extent than iNO. BAY 63–2521 has therapeutic potential and further studies are warranted.